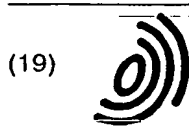


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(54) **STRETCHABLE PATCH**

(57) A stretch plaster comprising a support membrane having a thickness of 1 to 50  $\mu\text{m}$  and a drug containing adhesive layer having a thickness of 3 to 400  $\mu\text{m}$ , wherein

- (i) the support membrane comprising a copolymer of 0 to 90% by weight of vinyl acetate, 10 to 97% by weight of alkyl (meth)acrylate having 3 to 14 of a mean carbon number of alkyl group and 0 to 15% by weight of (meth)acrylic acid,  
(ii) the copolymer is cross-linked by polyvalent metal such as aluminum or a poly-functional chain compound, wherein the cross-linking ratio is 20% or more of the theoretical total number of carboxyl group of the copolymer when the polymer is cross-linked by the polyvalent metal such as aluminum,

and is 1 to 10 % expressed by copolymerized ratio of the poly-functional chain compound when the copolymer is cross-linked by poly-functional chain compound,

(iii) the support membrane has 150g or less of self adhesion shown by an adhesion between the support membranes and

(iv) the support membrane has 70% or more of an elasticity recovery when it stretches 10% of itself.

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## Description

## Technical Field

- 5 [0001] This invention relates to an excellently stretchable plaster. More particular, this invention relates to a plaster comprising an adhesive layer including adhesive substances formed on a flexible support with stretch. The plaster has no discomfort, fewer skin irritation and with particularly fewer inconvenience such as peeling from the skin, even when the plaster administers on body parts stretchable by body movement, for example, such parts as elbows or knees.

## 10 Background Art

[0002] There is a percutaneous drug administration route as one of the administration routes of drug other than per oral or injection etc. In the percutaneous drug administration, patients can administer drugs by themselves and drug concentration in body (plasma drug concentration) can be kept constant. Moreover the percutaneous drug administration is suitable for topical disease such as skin inflammation.

15 [0003] As one of the percutaneous drug administrations, the plaster, with which constant administration of drug is possible to attain and administration of drugs is simple, is used as an administration route widely.

[0004] A plaster has a merit which is not belonged to others. On the other hand, as a demerit of the plaster, it is pointed out that skin irritation at applied body parts is high, patients feel discomfort, patients can not handle easily to apply, the plaster is easy to peel from stretchable parts such as elbows or knees and the plaster has to be adhered on skin under clothes in order to conceal its prominentness.

20 [0005] To solve these demerits, many ideas have been proposed, however, the first requirement of the plaster is transdermal permeation of drugs. Therefore, after the first requirement is satisfied, these demerits of the plaster have to be decreased.

25 [0006] Since the above-mentioned demerits are mutually interrelated, it is not a easy task to solve all the problems at a time.

[0007] For example, it is well-known that a skin irritation is caused by damping occurred after excessive occlusion of the skin or by physical stimulation from hardness of the plaster, etc. Further, an excessively strong adhesion becomes a cause of skin irritation or discomfort. However, in case the occlusion is not sufficient, transdermal permeation of drugs becomes fewer and, therefore, it becomes necessary to increase the area of the plaster; this in turn, increases skin irritation and worsens the handling of the plaster

30 [0008] In addition, when the hardness of the plaster is lowered, the handling of the plaster becomes worse also. On the other hand, as the hardness of the plaster is made higher, the handling of the plaster becomes easier but the skin irritation increases.

35 [0009] In an ordinary skill of the drug design, it is usually maintained the property which wanted by patients prior to other properties, but for other properties, they are compromised in permissible range.

[0010] For example, in case of tape formulations or plasters for anti inflammatory analgesic, there are many such formulations in which; a web comprising stretch material such as urethane is adopted as a support in order to move together with the stretch of elbows and knees where inflammation is easy to occur; in order to increase the handlability of the plaster, etc., the thickness of supporter and drug containing adhesive layer is made large, hence, the it tends to be more stiff; in addition, adhesion of plasters, etc. are fixed as a little low rate to prevent an ache at removing plasters, etc.

40 [0011] However these tape formulations and plasters for anti-inflammatory analgetic have a problem of easy to peel. Generally, at the time of using these plasters, the peeling of the plaster is prevented by means of covering with net or bandage over the plaster. In addition, the plaster is changed as often as it peels.

45 [0012] There are many ordinary skills concerning these stretchable supports. However, a plaster satisfying both skin permeation of drug which is primary object of plaster and eliminating ordinary demerits is desired.

## Disclosure of Invention

50 [0013] The object of this invention is to provide a plaster having sufficient percutaneous absorption of drug, no discomfort even when it is applied on stretchable parts such as elbows or knees, adherence stability even without supporting net, and feeling no pains at removing from adhered parts of body.

[0014] Further the object of the present invention is to provide a plaster having particularly less skin irritation and less prominentness.

55 [0015] The inventors of this invention have achieved the present invention as a result of the earnest study based on a motivation making a plaster comprising safety adhesives.

[0016] Namely, this invention provides a stretch plaster comprising a support membrane having a thickness of 1 to

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50  $\mu\text{m}$  and a drug containing adhesive layer having a thickness of 3 to 400  $\mu\text{m}$ , wherein

- (i) the support membrane comprising a copolymer of 0 to 90% by weight of vinyl acetate, 10 to 97% by weight of alkyl (meth)acrylate having 3 to 14 of a mean carbon number of alkyl group and 0 to 15% by weight of (meth) acrylic acid,
- (ii) the copolymer is cross-linked by polyvalent metal such as aluminum or a poly-functional chain compound, wherein the cross-linking ratio is 20% or more of the theoretical values of total number of moles of carboxyl group of the copolymer when the polymer is cross-linked by the polyvalent metal such as aluminum, and is 1 to 10 % expressed by copolymerization ratio of the poly-functional chain compound when the copolymer is cross-linked by poly-functional chain compound,
- (iii) the support membrane has 150g or less of self adhesion shown by an adhesion between the support membranes and
- (iv) the support membrane has 70% or more of an elasticity recovery when it stretches 10% of itself.

#### Best Mode for Carrying Out the Invention

[0017] The support membrane of the present invention includes a copolymerized copolymer comprises 0 to 90 % by weight of vinyl acetate, 10 to 97 % by weight of (meth)acrylate alkyl ester having 4 to 14 of average carbon numbers and 0 to 15 % by weight of (meth)acrylic acid.

[0018] Hereinafter in the present invention, the copolymer which has no vinyl acetate is sometimes described as acrylic based copolymer and the copolymer which has vinyl acetate is sometimes described as vinyl acetate-acrylic based copolymer.

[0019] The acrylic based copolymer includes, for example, copolymer comprising (meth)acrylate alkyl ester and (meth)acrylic acid. The vinyl acetate-acrylic based copolymer includes, for example, a copolymer comprising vinyl acetate, (meth)acrylate alkyl ester and (meth)acrylic acid; a copolymer comprising vinyl acetate, (meth)acrylate alkyl ester, (meth)acrylic acid and vinyl ether such as vinyl butyl ether. Further the (meth)acrylate alkyl ester includes, for example, butyl(meth)acrylate, amyl(meth)acrylate, hexyl(meth)acrylate, heptyl(meth)acrylate, octyl(meth)acrylate, nonyl(meth)acrylate, decyl(meth)acrylate and 2-ethyl hexyl(meth)acrylate. In the present invention, when an acrylic based copolymer such as a copolymer of (meth)acrylate alkyl ester and (meth)acrylic acid is used, such (meth)acrylic acid is copolymerized 1 to 10 weight percent in advance in this acrylic based copolymer; and cross-linking of the acrylic based copolymer is carried out by either addition of polyvalent metal compounds or addition of 1 to 10 weight percent of poly-functional chain compounds at stage before the manufacture of the support membrane by coating. The polyvalent metal compound includes, for example, aluminum acetyl acetonate. The poly-functional chain compound includes, for example, 1,14-diglycidyl ether.

[0020] In addition, in case of using the acrylic based copolymer, the cross-linking ratio by using the polyvalent metal compound presents over 20% of ideal total molecular number of carboxylic base included in the acrylic based copolymer. It is preferable that the cross-linking ratio which shown by a polymerization ratio is 1 to 10% when the poly-functional chain compound is used.

[0021] Generally, an adhesion of copolymer comprising (meth)acrylate alkyl ester and (meth)acrylic acid is strong. When a copolymer which is used as an adhesive as usual is applied for a support membrane, a high cross-linking ratio is needed. However, the polymer tends to hard under the enough high cross-linking ratio.

[0022] In aforementioned view, preferable copolymer in the present invention is vinyl acetate-acrylic based copolymer comprising vinyl acetate, (meth)acrylate alkyl ester and (meth)acrylic acid.

[0023] It is preferable on the object of the present invention that the adhesion of the above-mentioned vinyl acetate-acrylic based copolymer obtained by copolymerization with vinyl acetate is weaker, a strength of the membrane is higher.

[0024] Preferable content of the vinyl acetate-acrylic based copolymer includes 25 to 85% by weight of vinyl acetate, 10 to 60% by weight of (meth)acrylate alkyl ester and 1 to 10% by weight of (meth)acrylic acid. Especially preferable content is 50 to 85% by weight of vinyl acetate, 10 to 40% by weight of (meth)acrylate alkyl ester and 1 to 10% by weight of (meth)acrylic acid.

[0025] Examples of the especially preferable (meth)acrylate alkyl ester include octyl(meth)acrylate and 2-ethyl hexyl (meth)acrylate. In addition, even when a vinyl acetate-acrylic based copolymer, (meth)acrylic acid is copolymerized 1 to 10 weight percent in advance in this vinyl acetate-acrylic based copolymer; and cross-linking of the acrylic based copolymer is possible to carry out by either addition of polyvalent metal compounds or addition of 1 to 10 weight percent of poly-functional chain compounds at stage before the manufacture of the support membrane by coating.

[0026] Example of the polyvalent metal compounds includes aluminum acetyl acetonate. Example of poly-functional chain compound includes 1,14-diglycidyl ether, etc.

[0027] The cross-linking ratio is 20% or more of the theoretical total number of moles of carboxyl groups in the vinyl

acetate-acrylic based copolymer when the polymer is cross-linked by the polyvalent metal. When the polymer is cross-linked by poly-functional chain compound, it is preferable to make the cross-linking ratio, which is shown by copolymerization ratio of the poly-functional chain compound, 1 to 10 %.

[0028] Especially, the vinyl acetate-acrylic based copolymer has a benefit that few gel-forming phenomenon by cross-linking presents and coating for the copolymer can be carried out smoothly when the polyvalent metal compounds such as aluminum acetyl acetonate are used.

[0029] The copolymers of the present invention, regardless whether they are acrylic base copolymer or vinyl acetate-acrylic copolymers, can be polymerized or added with other polymerizable compounds in accordance with the necessity.

[0030] In this invention, problems such as sticking of a supporter membrane of the plaster with other parts of the supporter after pressurized together may be occurred, when the plaster is applied on to a stretch part (a crook) especially, such as elbows or knees because the polymer usable as adhesives generally is adopted to the support membrane.

[0031] The inventors of the present invention has discovered that it is necessary to lower adhesion between the support membranes, namely self-adhesion, to solve the above-mentioned problem.

[0032] Concretely, the preferable self-adhesion is 150g or less. An adhesion of general adhesive layer for medical plaster is over 150g. Even minimum adhesion is 40g or more.

[0033] However, the adhesion between the adhesive layers namely self-adhesion, is much stronger than 150g. In many cases, the adhesion between the adhesive layers is 300g or more, besides it is strong enough to unremove. In the aforementioned uncross-linked state of adhesive, the adhesion between the adhesive layers is 300g or more. Therefore, the cross-linking ratio of the support membrane is fixed to achieve 150g or less of the self-adhesion.

[0034] The adhesion of this invention is measured according to the test method specified in "Plaster" of the Japanese Pharmacopoeia. An adhesion between the adhesive layers (self-adhesion) is also measured according to said test. The adhesion is measured by adhering a sample to a phenol resin plate. However, in case of measuring the adhesion between the adhesive layers (the self adhesion), it is measured by adhering between the support membranes.

[0035] In the present invention, a polymer (adhesive polymer) used as an adhesion as usual is adopted the support membrane. Therefore the plaster of the present invention can be stretched by moving of the skin, is not destroyed under using and has no peeling. On the other hand, toughness of the membrane tends to be small, because it is a usual physical property of adhesive and thickness of the membrane is small, and, therefore, problems, in which the plaster is impossible to remove from the skin once it was applied, may happen. To solve this problem, a proper strength is needed.

[0036] The present inventors found that the preferable strength of the support membrane of the present invention is 40g or more when it is tested according the testing method specified in "Plaster" of the Japanese Pharmacopoeia.

[0037] In order to obtain 40g or more of strength of the support membrane, it is preferable that a vinyl acetate-acrylic based copolymer containing a vinyl acetate is selected and the copolymer is cross-linked.

[0038] Additionally, 350,000 or more of average molecular weight of the vinyl acetate-acrylic based copolymer is preferable especially 450,000 or more is more preferable.

[0039] Further in view of less skin irritation, less prominentness and less discomfort, a thin support membrane is preferable. The thickness of the support membrane is 1 to 50  $\mu\text{m}$ , especially 5 to 30  $\mu\text{m}$  of thickness is more preferable.

[0040] In the support membrane of the present invention, an elasticity recovery is needed to fix stably and comfortably on parts stretching heavily such as elbows or knees. Concretely, the elasticity recovery is needed that in case the support membrane stretches 10% of itself (10% of stretch corresponds to a skin stretch in daily life), it recovers 70% of its stretched parts. When the elasticity recovery is low, some problems may happen. These problems are that the plaster peels, the plaster removes and the plaster is prominent on the skin.

[0041] In order to improve handling of the plaster, a cover layer can be laminated opposite side of the drug containing adhesive layer of the plaster comprising the support membrane and the drug containing adhesive layer in the present invention.

[0042] In this case, it is needed to select the cover layer which has 50g or less of adhesion with the support membrane.

[0043] The cover layer includes; a separate liner film comprising polyester, polyethylene, polypropylene, vinyl chloride or polyethylene vinyl acetate; a separate liner paper; a web comprising polyester, nylon, urethane, or silicon having 5 to 300  $\text{g/m}^2$  unit area weight; a knitted fabric; a woven fabric; or a non-woven fabric.

[0044] The thickness of the cover layer is 10 to 100  $\mu\text{m}$  preferably.

[0045] In addition, the cover layer can be laminated the support membrane and cut into the same area or the support membrane. When a part of the cover layer such as a vertical part or a horizontal part is 3 to 20 mm bigger than the support membrane, the handling of the plaster is improvable. When length and breadth of the cover layer is 3 to 20 mm bigger than the support membrane, also the handling of the plaster is improvable.

[0046] The plaster of the present invention can be attached with a separate liner (liner sheet) on a surface of the drug containing adhesive layer.

[0047] In case of the cover layer is cut as the same area size of the support membrane, a splitting cut line was formed

on the center (10 to 90% area of vertical direction) of the cover layer. Therefore only the liner can be removed firstly in case of administration. On the other hand, when a part of the cover layer is bigger than the support membrane, the split line may not be needed.

[0048] Moreover the cover layer can cover the entire support membrane or can be formed on a part of the support membrane as the support membrane does not curl.

[0049] The cover layer can be formed after the plaster was manufactured. Or the cover layer can be formed by coating with polymer in the process of manufacturing of the plaster.

[0050] Concretely, the support membrane in proper thickness is formed on the cover layer by coating with the dope such as the acrylic based copolymer comprising (meth)acrylate alkyl ester and (meth)acrylic acid; the vinyl acetate-acrylic based copolymer comprising vinyl acetate, (meth)acrylate alkyl ester and (meth) acrylic acid; and the vinyl ether comprising butyl vinyl ether. A combination of the cover layer and the support membrane, which having more uniformity and high stability, can be made by the above-mentioned method.

[0051] It is effective in case a web is used as the cover layer that the web is laminated with the support membrane and then the resultant is heated at 50 to 130 °C and pressed.

[0052] The drug containing adhesive layer of the present invention comprises the same adhesion as the support membrane's mainly. Also the drug containing adhesive layer can be added to other component.

[0053] The drug containing adhesive layer presents in order to fix the plaster of the present invention and be absorb the drug percutaneously.

[0054] The support membrane of the present invention fills a role of covering the drug containing adhesive layer and the other component of the plaster or other composite parts as a cover membrane of the plaster. On the other hand, the required property of the drug containing adhesive layer is different from that of the support membrane, therefore the drug containing adhesive layer has no limitation such as the strength of the self-adhesion.

[0055] The adhesives of the drug containing adhesive layer includes a vinyl acetate based adhesive (EV) comprising 25 to 85 % by weight of vinyl acetate, 10 to 60% by weight of alkyl (meth)acrylic acid having 3 to 14 of a mean carbon number and 1 to 10% by weight of (meth)acrylic acid; an acrylic based adhesive (AP) comprising 50 to 97% by weight of (meth)acrylate alkyl ester and 1 to 10% by weight of (meth)acrylic acid; and a mixture of EV and AP based adhesive. Especially EV is a preferable component, because EV is easy to be miscible with the drug generally, is highly safe to the skin and has a low adhesion. More preferable ratio of EV to AP in the mixture of EV and AP is 0.1 to 20.

[0056] The alkyl (meth)acrylic acid having 3 to 14 of a mean carbon number includes, for example, butyl(meth)acrylate, amyl(meth)acrylate, hexyl(meth)acrylate, octyl(meth)acrylate, nonyl(meth)acrylate, decyl(meth)acrylate and 2-ethyl hexyl(meth)acrylate.

[0057] The adhesive of the drug containing adhesive layer is not needed to be the same components of the support membrane. Adhesives such as an ordinary acrylic based, a rubber based, a silicon based or a vinyl acetate based adhesives can be adopted.

[0058] Since the objectives in this invention are less skin irritation, less discomfort and less ache under peeling, a low adhesion of the drug containing adhesive layer is preferable. An adhesion of the general plasters is more than 150 g, which is the specification of the Plaster in the Japanese Pharmacopoeia. The value is needed to prevent peeling of the plaster from the skin. The plaster of the present invention is not easy to peel, because the stretch support membrane is adopted. To prevent from the ache under peeling, a preferable adhesion of the present plaster is 150g or less, especially, 30 to 120g is more preferable.

[0059] However the adhesion to the skin depends on the duration of administration, and the adhesion of Plaster of the Japanese Pharmacopoeia is a value of adhesion to a phenol resin board. Therefore we don't need to stickle about the value mentioned above.

[0060] The adhesion of the present plaster to the skin can be smaller than that of the ordinary plaster. Though the present plaster can prevent the ache of patients under peeling, the present plaster is harder to peel off than the ordinary plaster.

[0061] The drug in the present invention includes anti inflammatory analgetic agent such as salicylate esters, indomethacin and ketoprofen, hormones for dermatosis such as valeric acid, betamethasone and dexamethasone, vitamins such as vitamin A, vitamin C and vitamin E, coronary vasodilators such as isosorbide nitrate and nitroglycerin, sedative drugs/ anxiolytics such as brotizelam and triazolam, anti-hypertensives/circulatory agents such as propranolol, antibiotics, anti-tussives/bronchodilators such as tulobuterol hydrochloride, ambroxol hydrochloride, ipratropium bromide, tranilast, azelastine hydrochloride and clenbuterol hydrochloride, anti-ulcer agents such as clobopride malate, famotidine and lansoprasole, hormones such as estradiol, anti-allergic agents such as feroxyphenazine and anti-psoriasis agents such as tacalcitol. However the drug of the present invention does not limited to these drugs above mentioned.

[0062] Further components except the aforementioned medical drug can be used for beauty, health and moisturize. Examples of these components include urea, liquid paraffin, polyethylene glycol, glycerin, propylene glycol, surfactants, squalene, squalane, cayenne pepper, extract from natural products such as herb, zinc oxide, titanium oxide, living

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rock, rock having far-infrared ray, ceramic, silk fiber or their component.

[0063] The plaster of this invention has extremely low discomfort, so the plaster can be adhered stably on crooks such as elbows or knees. Additionally the plaster is not prominent on the skin. Therefore the plaster has benefits in the object of beauty, health and moisturize. And ordinary plasters have never had these benefits.

[0064] In the present plaster, volume of drugs and ratio of drugs are extremely flexible. In many cases of the ordinary plasters, to achieve high percutaneous absorption of drug, drug concentration of the plaster is high and the third component is added. Therefore the adhesion of the adhesive layer becomes low, so volume or ratio of third component is limited. However in the plaster of the present invention, the adhesion to the skin is comparatively low, so the volume of drugs and the ratio of drugs are extremely flexible.

[0065] Generally, volume of drug of plasters is 0.01 to 30% by concentration of the adhesion. But, for example, in case of tacalcitol, plasters having 0.0001 to 0.01% of tacalcitol have pharmacological effects, therefore the drug concentration can be fixed by drug effect of active component and indication of drug.

[0066] In percutaneous absorption, the drug can be prevented from the first pass effect, so the drug content which can show the drug effect is known as same content or 1/100 compared to administration routes such as per oral administration. However, ratio of percutaneous absorption is influenced by drug concentration in the adhesive layer and a drug concentration gradient in the skin, which is a role of barrier of drug permeation. Hence, it is said that the drug content in pharmaceutical composition is required to be the same amount or 1000 times of the amount of the drug absorbed into the body.

[0067] Namely, the range of the absolute bioavailability (BA) by percutaneous absorption is 0.1 to 100%, actually it is 0.1 to 50%, and generally, in consideration of these values, drug content and concentration in pharmaceutical composition is determined.

[0068] It is possible to set the drug containing adhesive layer in these s invention at 3 to 400  $\mu\text{m}$  in thickness.

[0069] Generally, an adhesion of plasters is getting stronger according to thickness of the drug containing adhesive layer. From the view of adhesion, preferable thickness of adhesive is 10  $\mu\text{m}$  or more, and 30  $\mu\text{m}$  or more ordinary. However in the present invention, it is possible that the thickness of adhesive layer is set at less than ordinary ones, because it is allowed to make the adhesion to the skin to remain low. Additionally, a maximum of preferable thickness is 100  $\mu\text{m}$  or 200  $\mu\text{m}$  in ordinary plaster, however, the present plaster can keep its ability as a pharmaceutical product, even the drug containing adhesive layer is thicker than the ordinary, because the supporter of the present invention is thin. Especial preferable thickness of the drug containing adhesive layer in this invention is 5 to 200  $\mu\text{m}$ .

[0070] In the present plaster, for improvement of the hardness under administration, for raise of the beauty or for increasing of drug permeation to the skin, it is possible to divide into several parts the drug containing adhesive layer itself or an inside thereof. On the other hand, it is possible to imbed other components of plasters, making the plaster a multi-laminated layer, another bases can be buried as lamination layers.

### Examples

[0071] Following examples illustrate the present invention. However, it should not be understood that these examples are given to limit the scope of the invention.

In these examples, parts, % and ratio are shown by weight.

[0072] The following is one of the synthetic method of vinylacetate based adhesive (EV-51) used in these examples.

[0073] 70% of vinyl acetate, 27.5 parts of 2-ethyl hexyl acrylate, 2.5 parts of acrylic acid, 1.0 parts of benzoyl peroxide and 200 parts of ethyl acetate are set in the reaction vessel with a reflux condenser and mixer. They were polymerized by gradually mixing for 18 hours under  $\text{N}_2$  gas and 60° C. Resulted vinyl-acetate based copolymer had 650,000 of molecular weight. The concentration of the solution is prepared to be 30% by addition of ethyl acetate.

[0074] Also the following is one of synthetic method of acrylic based (AP-52) adhesive used in the examples.

[0075] 90 parts of 2-ethylhexyl acrylate, 7.5 parts of methyl methacrylic acid, 2.5 parts of acrylic acid, 1.0 part of benzyl peroxide and 300 parts of ethyl acetate acid as set in the reaction vessel with a reflux condenser and mixture. Then polymer was produced by gently mixing for 17 hours under  $\text{N}_2$  gas and 60 °C. The obtained acrylic based copolymer had 580,000 of mean molecular weight. The concentration of the polymer dope was prepared to be 20% by addition of ethyl acetate.

### Example 1

#### <Preparation of the support membrane>

[0076] 100 parts of 30% ethyl acetate solution of vinyl acetate based adhesive (EV-51) was added to 0.675 parts of aluminum acetyl acetate was dissolved in 12 parts of acetyl acetone, and then mixed well. The resulted solution was coated on 75  $\mu\text{m}$  thickness of polyethylene telephthalate liner to be 10  $\mu\text{m}$  of thickness after drying. After drying for 1

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minute at 70 ° C, for 1 minute at 80 ° C and for 1 minute at 120 ° C, obtained 10 µm thickness of the support membrane coated 75 µm thickness of polyethylene telephthalate liner.

[0077] In this case the cross-linking ratio of EV-51 was 60%. It was calculated on the supposition that one mole of trivalent of aluminum bind to 3 moles of carboxyl group.

[0078] The strength of obtained support membrane with liner was 12g.

#### <Preparation of a drug containing adhesive layer>

[0079] 233 parts of 30% EV-51 ethyl acetate solution, 175 parts of AP-52 ethyl acetate solution, 30 parts of isopropyl myristate and 0.263 parts of indomethacin were well mixed. Then the solution was coated on the another 75 µm thickness of polyethylene telephthalate liner, and dried for 2 minutes at 70 ° C, for 2 hours at 80 ° C and for 2 minutes at 110 ° C to obtain the 100 µm thickness of the drug containing adhesive layer.

[0080] The adhesion of the obtained adhesive layer was 25g.

[0081] Resulted the adhesive layer with a liner is laminated on the surface of the support membrane with the liner. Then it was cut out into a rectangle shape with the 100 mm x 70 mm size. Subsequently, splitting cut line was formed on the surface of the liner which adhered on one side of the adhesive layer, the indomethacin containing plaster was obtained.

[0082] The indomethacin containing plaster was cut at 1.13 cm<sup>2</sup> of area and adhered on a back of the hairless rat whose hair was shaved for 21 hours, and then the amount of drug absorbing was determined; the amount of drug absorbing was about 10 % and the amount of drug absorbed was equivalent to commercially available indomethacin plaster. Under adhering of the plaster in this test, the protecting material was not required. On the other hand, the commercial plaster was required by the protection with gauze.

[0083] The removal strength between the support membranes of a commercial indomethacin plaster was 23g.

#### Experiments 1 to 6

[0084] In the preparation of the support membrane, several of support membranes which have various cross-linking ratio were produced by changing the content of alminum acetyl acetate in the comparison of example 1. Table 1 shows their cross-linking ratio and removal strength.

#### Experiment 7

[0085] To investigate the use feeling of plaster of the present invention, placebo plasters, which do not contain indomethacin, were manufactured according to example 1. 100 mm x 70 mm area of the placebo plasters were adhered on human elbows for 24 hours. (n=3) While adhering, there were no peeling off of plasters, they felt a little uncomfortable, and when removing, it was confirmed that they felt no aches and the support membrane kept good shape.

#### Comparative example 1

[0086] According to example 1, the indomethacin containing plaster was manufactured except alminum acetyl acetate in the preparation steps of the support membrane. When the product was adhered to rat, it was difficult because of adhesion of support membrane. In this case the removal strength between the support membranes (self-adhesion) was 500g or more.

#### Experiment 8

[0087] To investigate the use feeling while adhering, the placebo plasters according to example 1 except indomethacin were manufactured at the area of 100 mm x 70 mm. An adhering test of the placebo plaster on human elbow for 24 hours was planed. However the placebo plasters could not be adhered on human elbow, because the adhesion of the support membrane caused the adhesion between the support membranes and the placebo plaster could not keep shape of itself for adhering at human elbows.

Table 1 :

Cross-linking ratio and peeling strength between the support membranes (self-adhesion)	
Cross-linking ratio (%)	Self-adhesion (g)
6	500 or more

Table 1 : (continued)

Cross-linking ratio and peeling strength between the support membranes (self-adhesion)	
Cross-linking ratio (%)	Self-adhesion (g)
10	370
20	131
40	62
60	12
100	6

## Claims

1. A stretch plaster comprising a support membrane having a thickness of 1 to 50  $\mu\text{m}$  and a drug containing adhesive layer having a thickness of 3 to 400  $\mu\text{m}$ , wherein

(i) the support membrane comprising a copolymer of 0 to 90% by weight of vinyl acetate, 10 to 97% by weight of alkyl (meth)acrylate having 3 to 14 of a mean carbon number of alkyl group and 0 to 15% by weight of (meth)acrylic acid,

(ii) the copolymer is cross-linked by polyvalent metal such as aluminum or a poly-functional chain compound, wherein the cross-linking ratio is 20% or more of the theoretical total molar number of carboxyl group of the copolymer when the polymer is cross-linked by the polyvalent metal such as aluminum, and is 1 to 10 % expressed by copolymerized ratio of the poly-functional chain compound when the copolymer is cross-linked by poly-functional chain compound,

(iii) the support membrane has 150g or less of self adhesion shown by an adhesion between the support membranes and

(iv) the support membrane has 70% or more of an elasticity recovery when it stretches 10% of itself.

2. The stretch plaster according to claim 1, wherein the support membrane has 3 to 30 m in thickness, the drug containing adhesive layer has 5 to 200 m in thickness and the support membrane comprises a vinyl acetate-acrylic based copolymer obtained by copolymerization of 25 to 85% by weight of vinyl acetate, 10 to 60% by weight of alkyl(meth)acrylate having 3 to 14 of a mean carbon number of alkyl group and 1 to 10% by weight of (meth)acrylic acid.
3. The stretch plaster according to claim 2, wherein the vinyl acetate-acrylic based copolymer is cross-linked by a polyvalent metal such as aluminum, wherein the cross-linking ratio is 20% or more of the theoretical total molar numbers of carboxyl group of the copolymer, and the self adhesion expressed by an adhesion between the support membranes is 100g or less.
4. The stretch plaster according to any one of claims 1 to 3, wherein the support membrane has a cover layer on the other side of the drug containing adhesive layer for improvement of its handling, and has a 50g or less of adhesion with the support membrane.
5. The stretch plaster according to any one of claims 1 to 4, wherein the drug is selected from the group consisting of anti inflammatory analgetic agent, hormones for dermatosis, vitamins, coronary vasodilators, sedative drugs, anxiolytics, anti-hypertensives, circulatory agents, antibiotics, anti-tussives, bronchodilators, anti-ulcer agents, hormones, anti-allergic agents and anti-psoriasis agents.
6. The stretch plaster according to any one of claims 1 to 5, wherein the drug is selected from the group consisting of salicylate esters, indomethacin, ketoprofen, valeric acid, betamethasone, dexamethasone, vitamin A, vitamin C, vitamin E, isosorbide nitrate, nitroglycerin, brotizelam, triazolam, propranolol, tulobuterol hydrochloride, ambroxol hydrochloride, ipratropium bromide, tranilast, azelastine hydrochloride, clenbuterol hydrochloride, clebopride malate, famotidine, lansoprasole, estradiol, feroxy phenazine and tacalcitol.

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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP01/01691

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> Int.Cl. <sup>7</sup> A61K9/70, A61K47/32, A61K31/60, A61K31/405, A61K31/192, A61K31/573, A61K32/07, A61K31/375, A61K31/34, A61K31/21, A61K31/551, A61K31/138, A61K31/137 According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) Int.Cl. <sup>7</sup> A61K9/70, A61K47/32, A61K31/60, A61K31/405, A61K31/192, A61K31/573, A61K31/07, A61K31/375, A61K31/34, A61K31/21, A61K31/551, A61K31/138, A61K31/137 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP, 10-226638, A (Teisan Seiyaku K.K.), 25 August, 1998 (25.08.98), (Family: none)	1-6
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 23 May, 2001 (23.05.01)		Date of mailing of the international search report 05 June, 2001 (05.06.01)
Name and mailing address of the ISA/ Japanese Patent Office		Authorized officer
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